

Therapy for HBV and HCV: An Optimist's Perspective

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VIRAL HEPATITIS

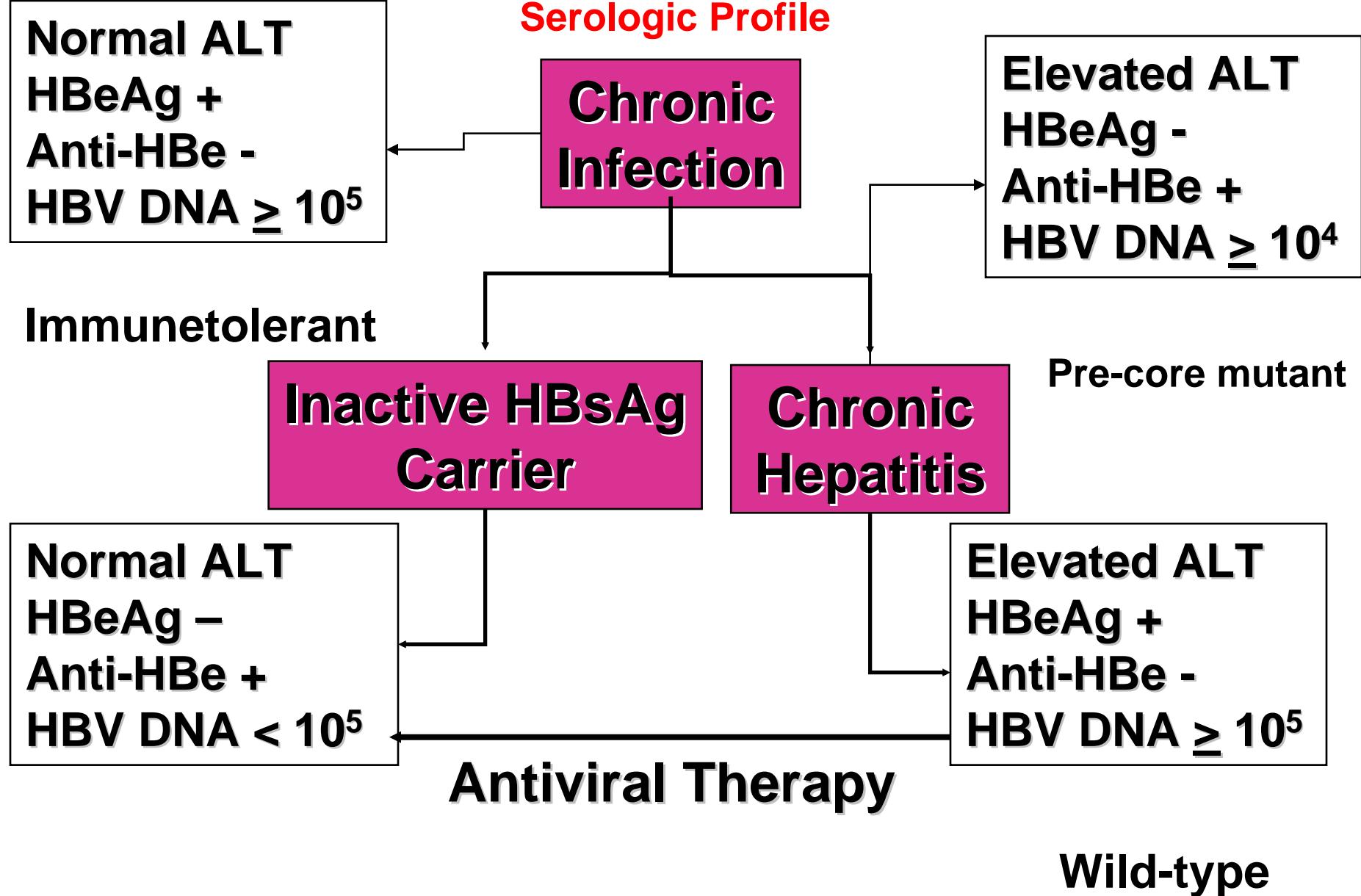
Satanic Serologies

- Hepatitis B surface antigen
HBsAg = Current Infection
- Hepatitis B surface antibody
Anti-HBs = Resolution
- Hepatitis B core antibody
HBcAb = Exposure (IgM vs IgG)
- Hepatitis B e antigen
HBeAg = Activity (replication)
- Hepatitis B e antibody
Anti-HBe = Resolution of Activity
- HBV DNA

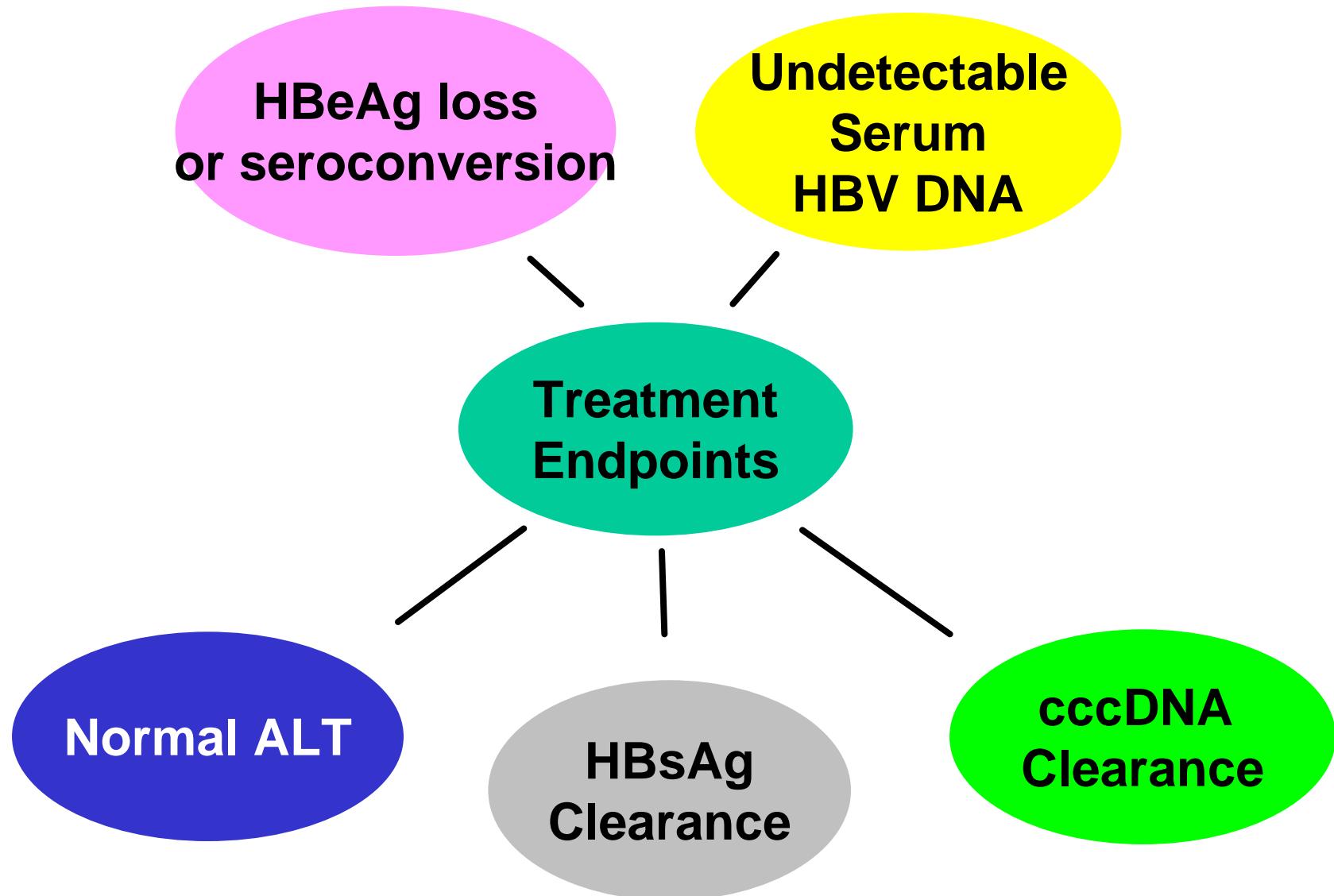


Chronic Hepatitis B

Serologic Profile

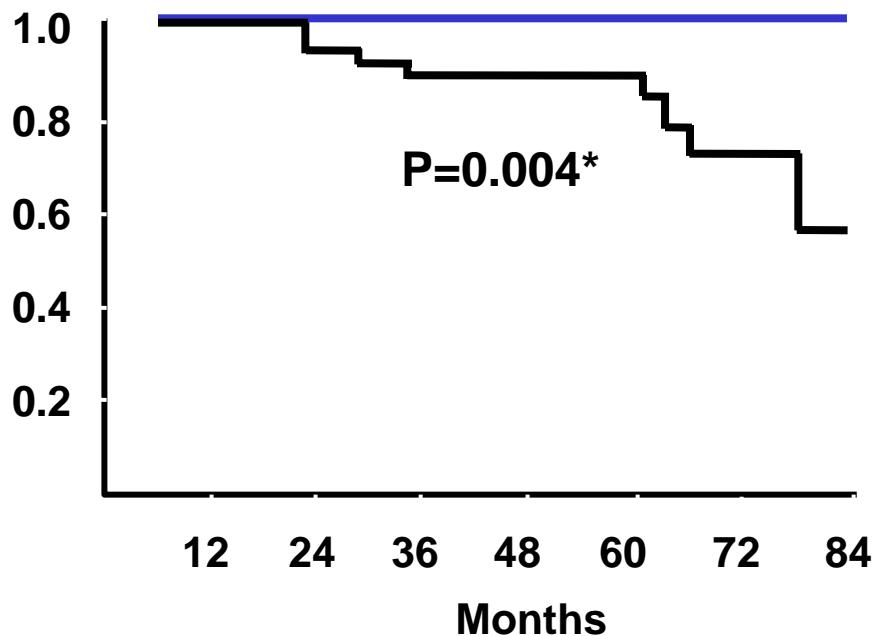


Viral and Serologic Treatment Endpoints in Chronic Hepatitis B

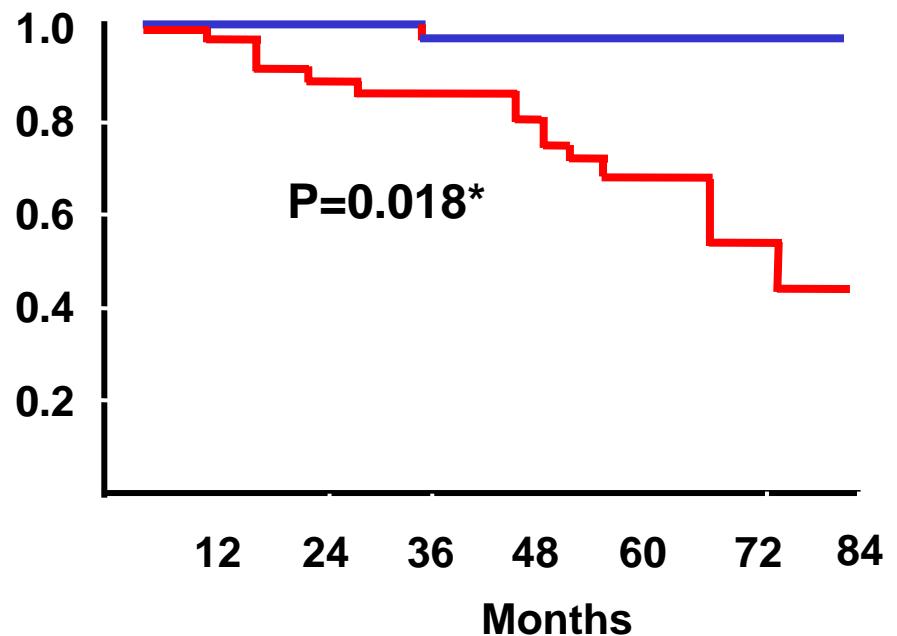


HBeAg Seroconversion with IFN α Therapy is Associated with Improved Clinical Outcome

Proportion of patients surviving



Proportion free of hepatic complications

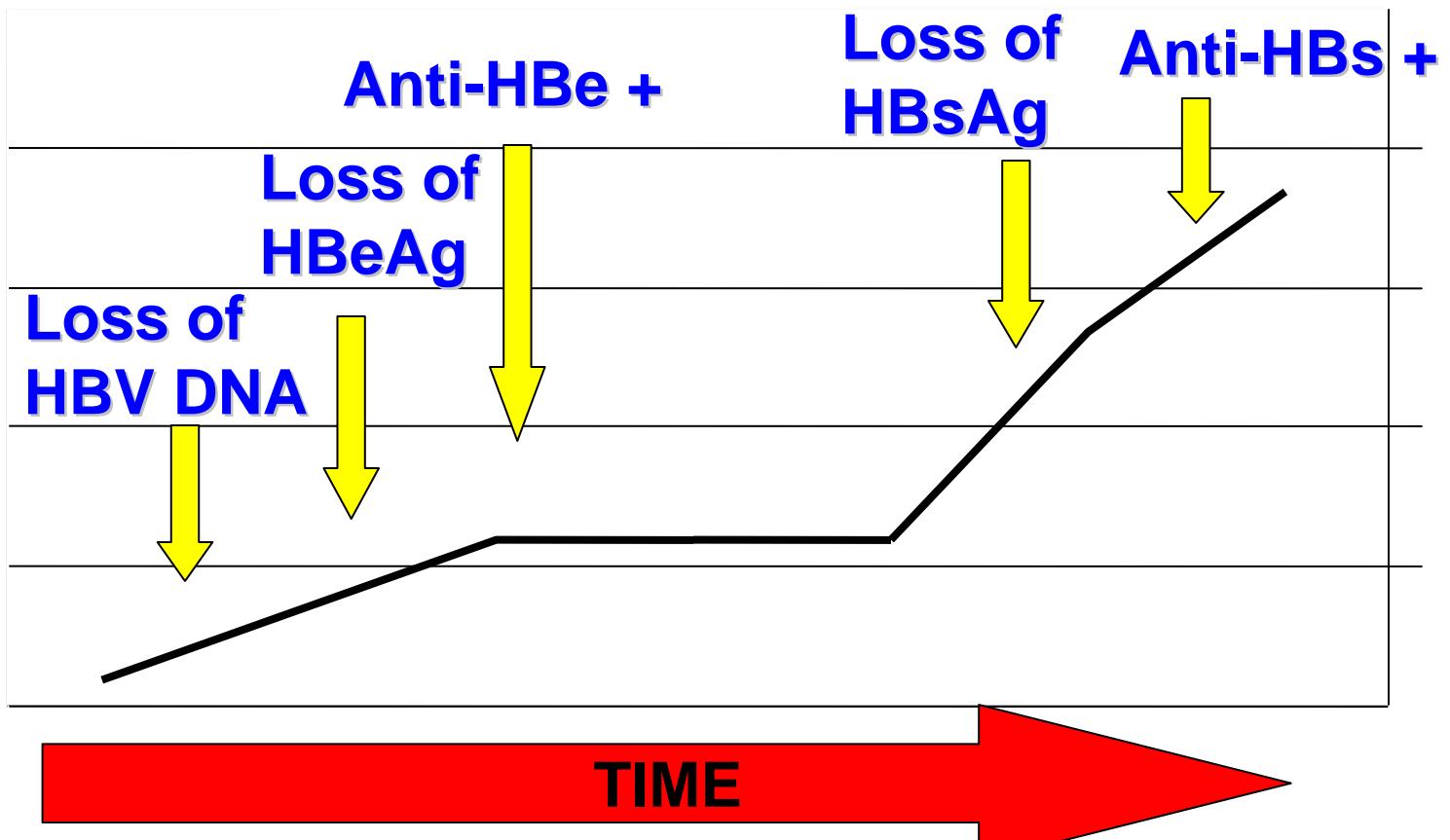


— IFN α -treated WITH HBeAg clearance

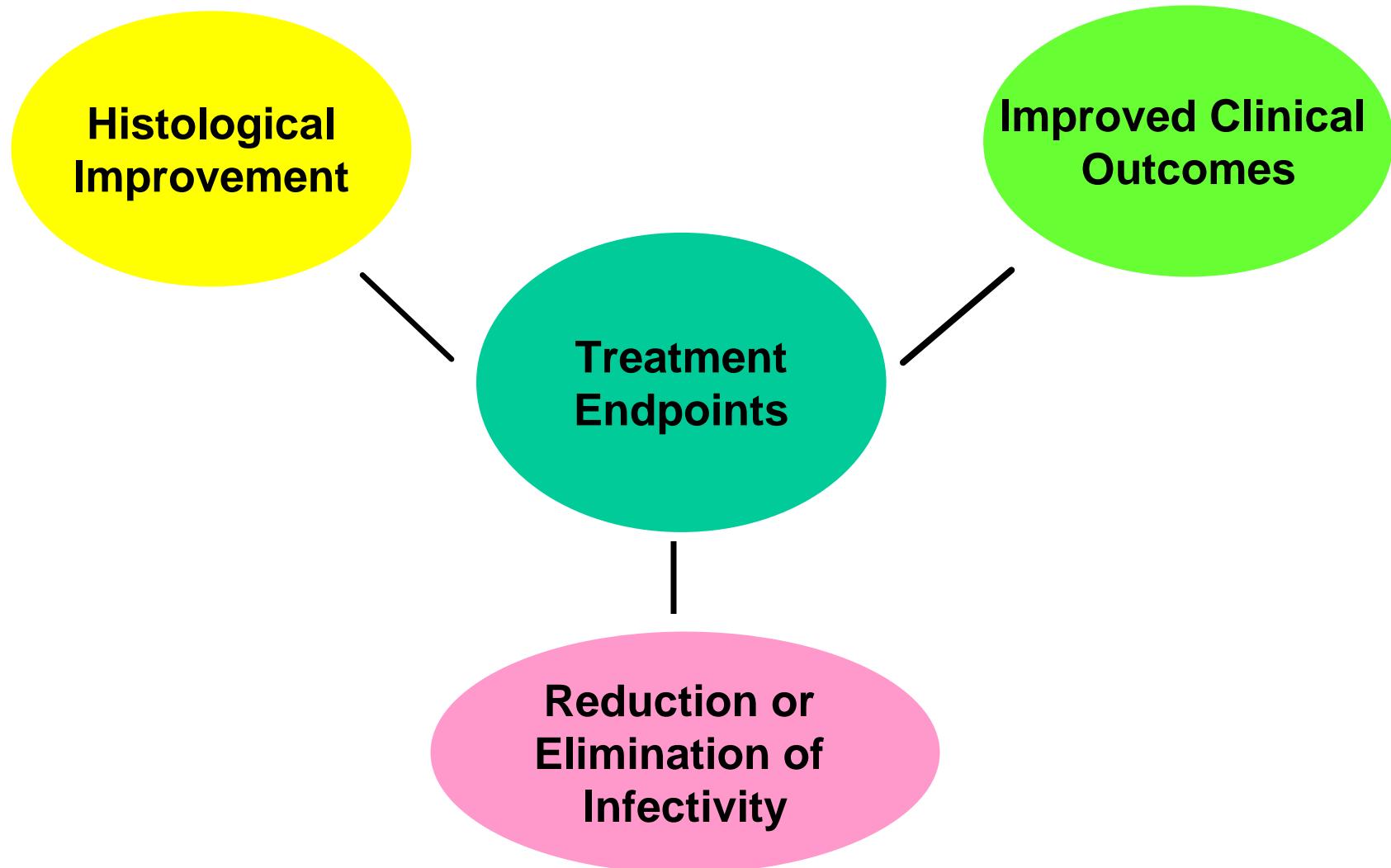
— IFN α -treated WITHOUT HBeAg clearance

*According to the proportional hazards model

Evolution of Therapeutic Endpoints



The Ultimate Treatment Endpoints in Chronic Hepatitis B



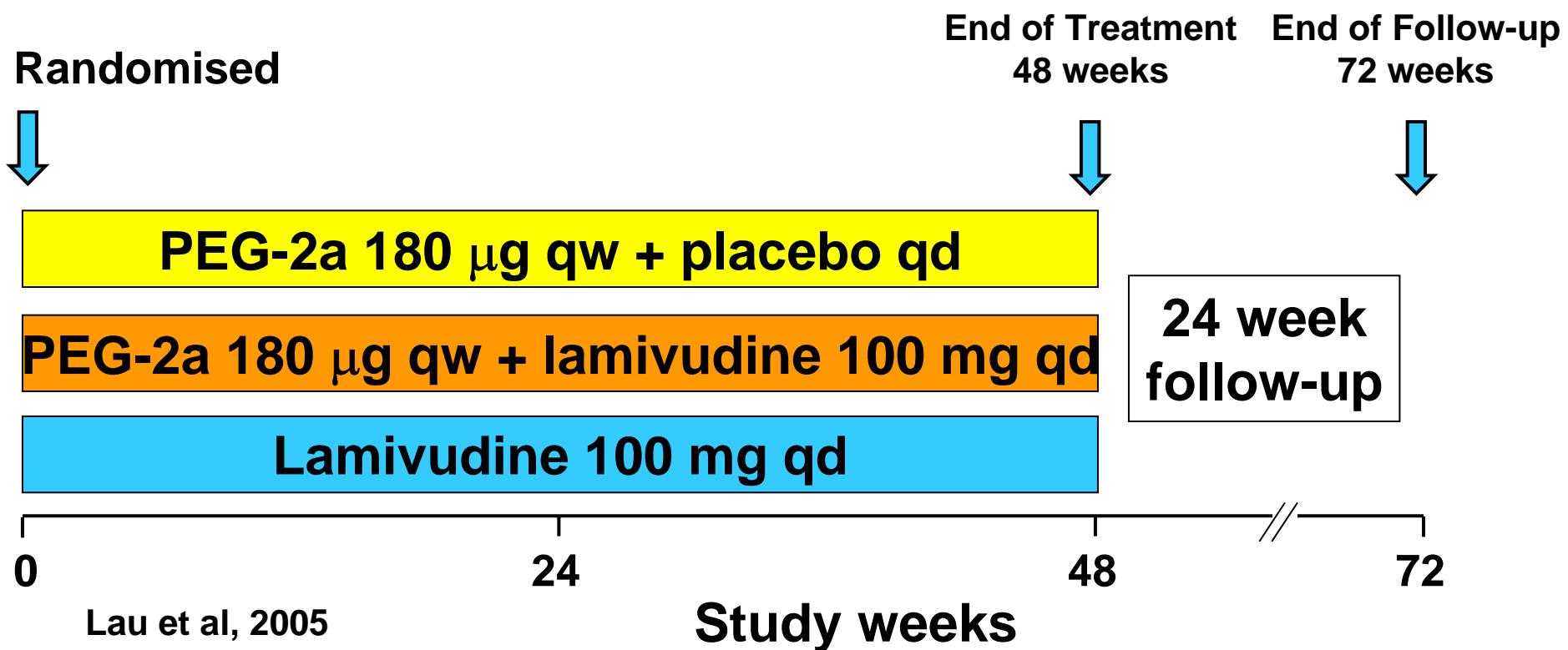
New HBV Therapies Under Development

FDA-Approved	Phase III	Phase II	Phase I
Interferon alfa-2b Lamivudine Adefovir Entecavir Peginterferon alfa-2a	Emtricitabine Tenofovir Telbivudine (LdT)	Clevudine Elvucitabine Valtorcitabine (LdC) Amdoxovir (DAPD) Racivir (RCV) BAM 205 HepX-B (XTL-001) HE2000 Thymosin-alpha Theradigm EHT 899	MCC 478 MIV 210 Ramofovir HBV Vaccine

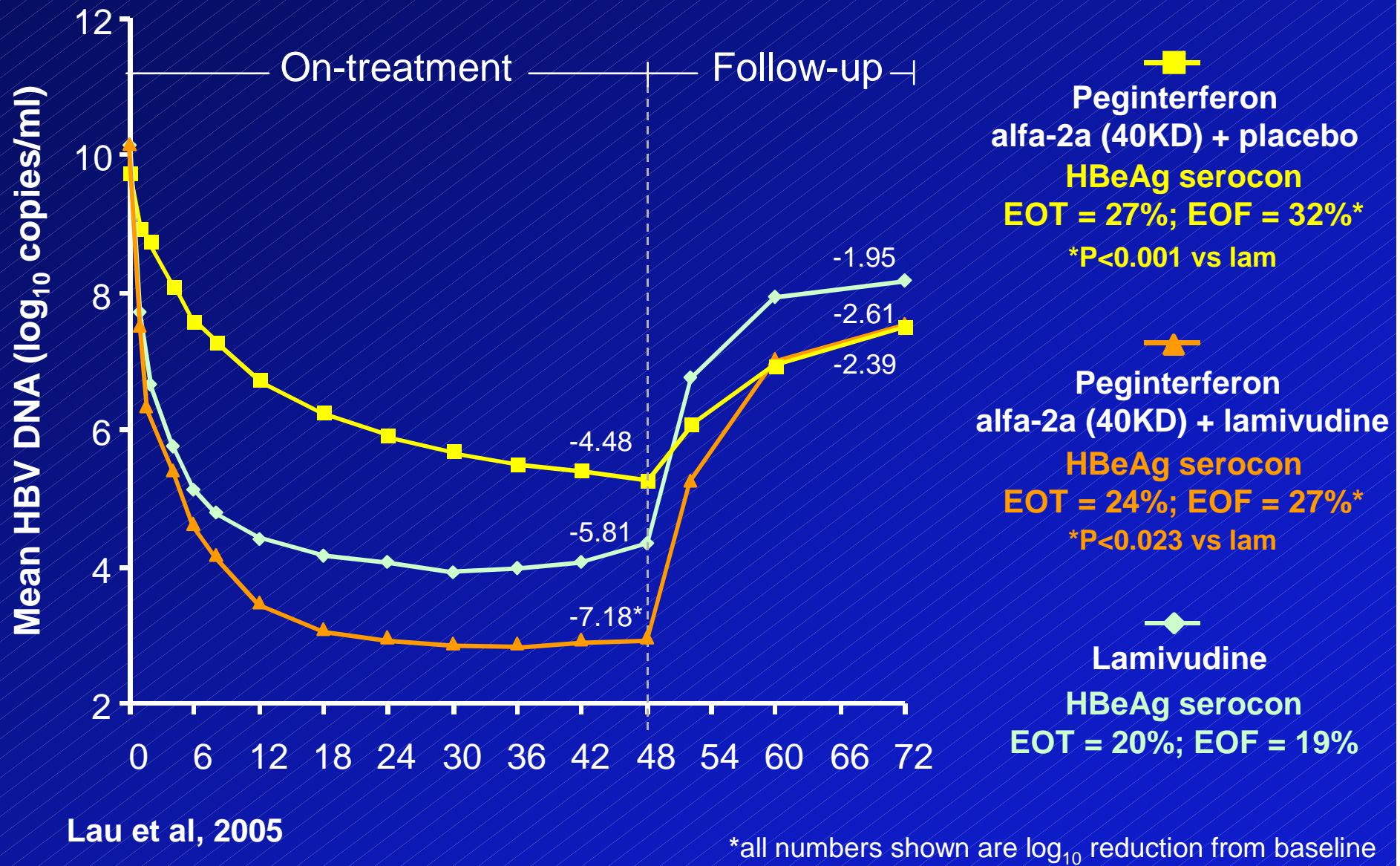
PEG-2a for HBV

Patients with HBeAg-positive CHB were randomised using a 1:1:1 ratio

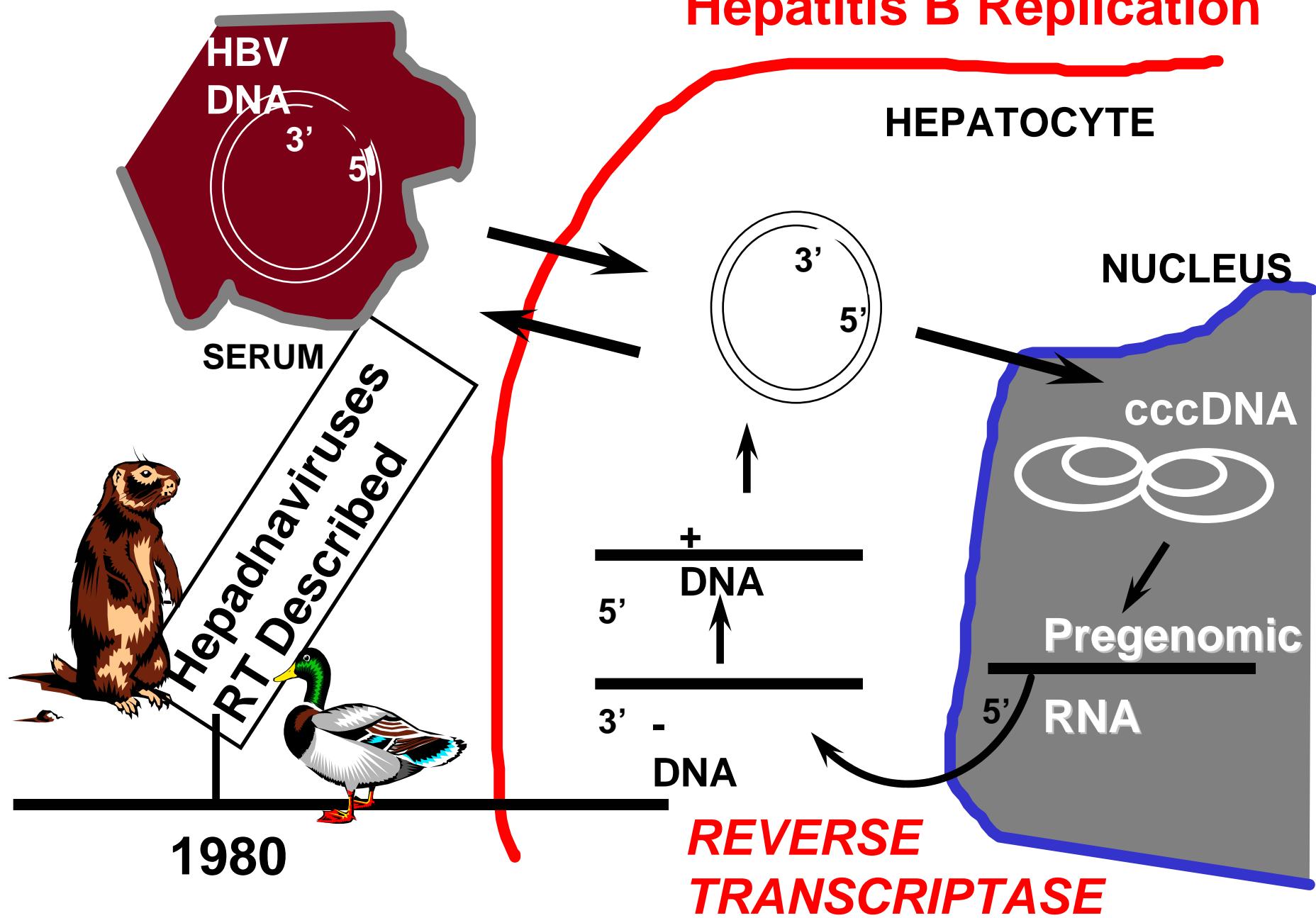
ITT population: n=814



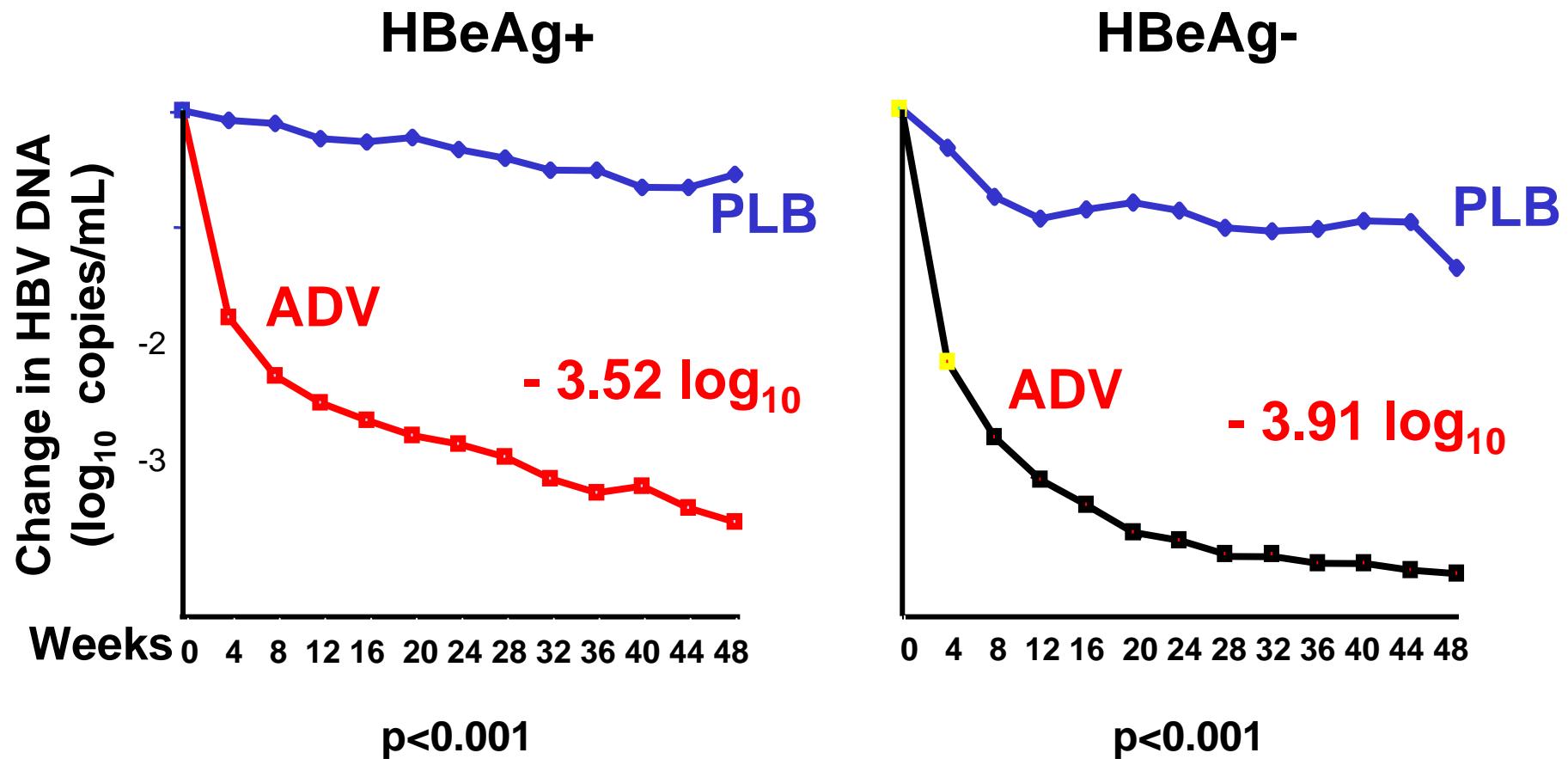
PEG-2a and HBV



Hepatitis B Replication

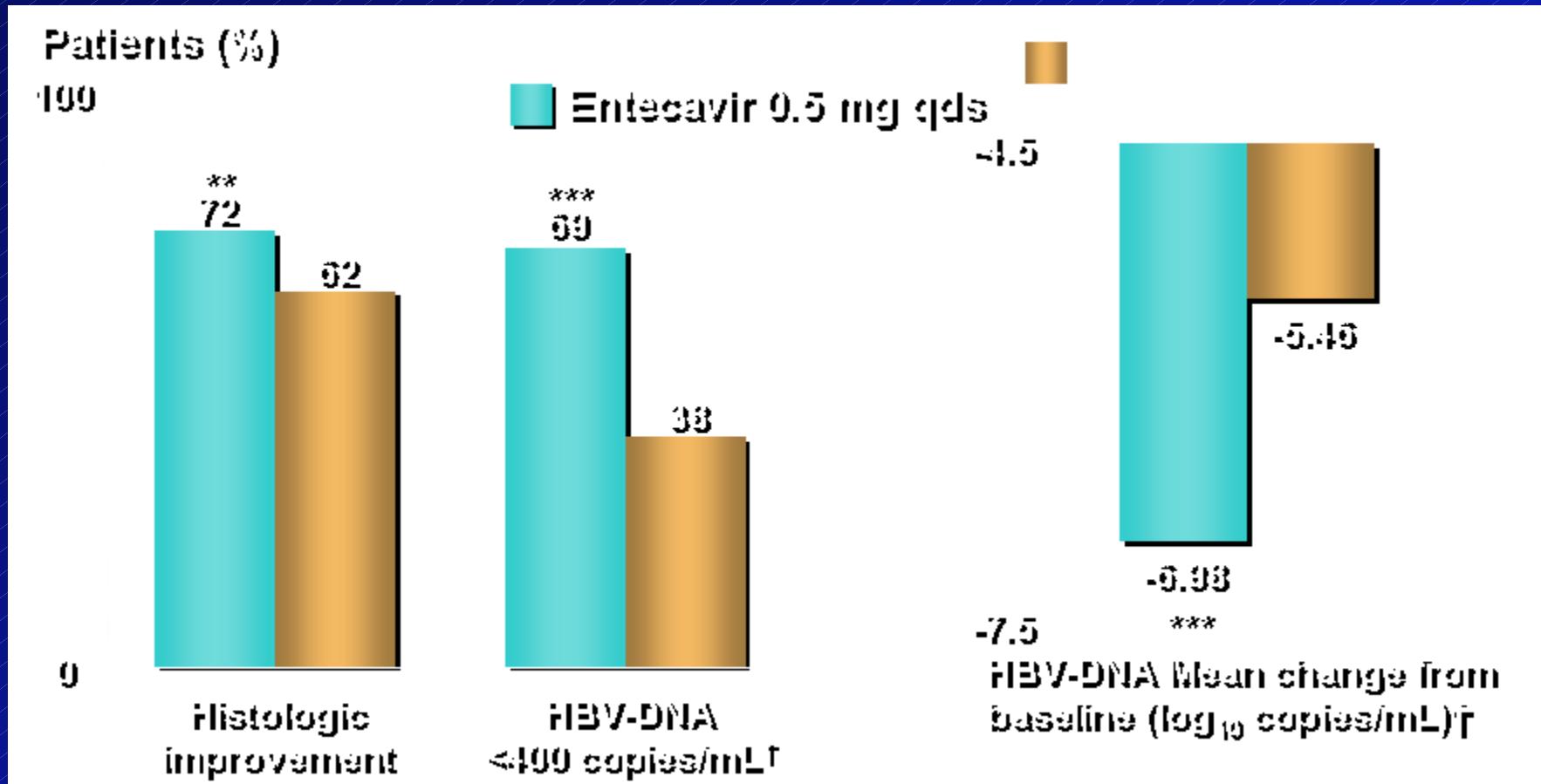


Adefovir
Median Change in HBV DNA



Marcellin et al, 2003
Hadziyannis et al, 2003

Entecavir for HBeAg-positive disease: Results at week 48



**p<0.01 vs lamivudine

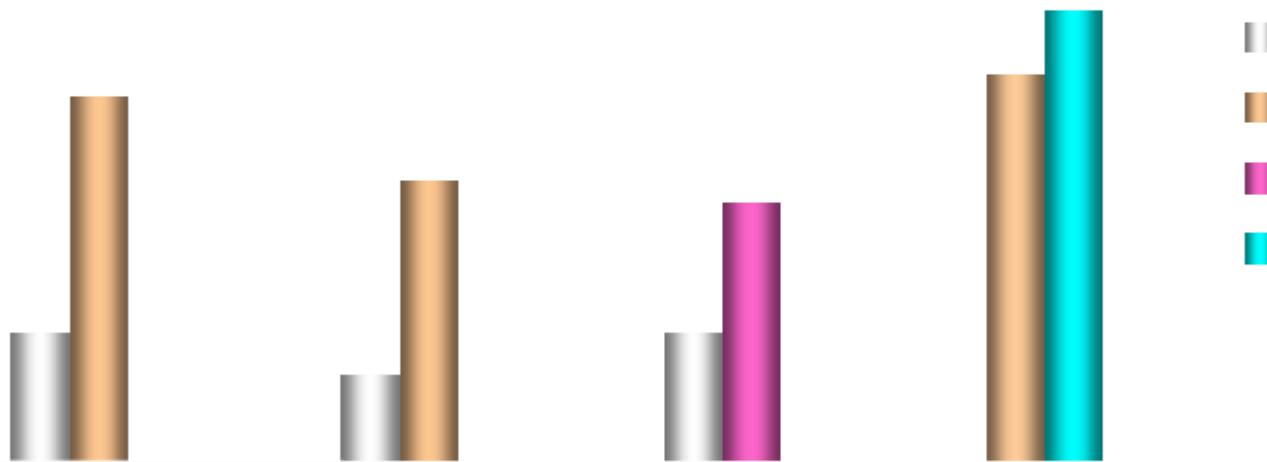
***p<0.0001 vs lamivudine

†HBV-DNA assays by PCR

Chang, Gish et al, AASLD, 2004.

Rates of HBeAg seroconversion in pivotal clinical trials of oral therapy

HBeAg seroconversion at 1 year (%)



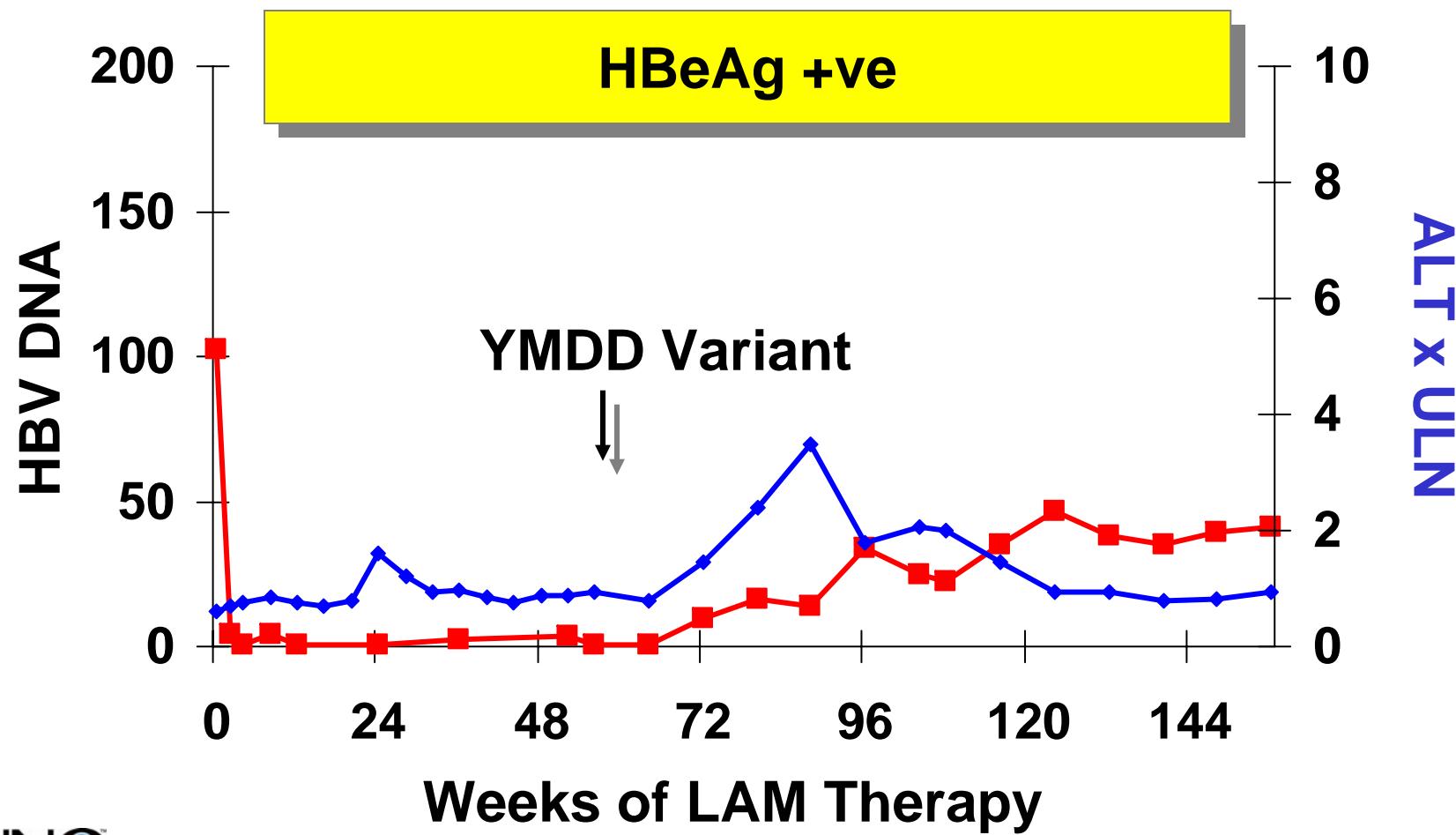
Dienstag et al, *N Engl J Med* 1999; 341: 1256

Lai et al, *N Engl J Med* 1998; 339: 61

Marcellin et al, *N Engl J Med* 2003; 348: 808

Chang et al, *Hepatology* 2004; 40(4 Suppl.): 193A

YMDD Mutant Clinical Course



Treatment Algorithm HBeAg +

HBeAg Status	HBV DNA	ALT	Possible Strategy
Positive	< 10 ⁵	Normal	Monitor q6-12 months ? therapy w/high HAI
Positive	≥10 ⁵	Normal	Low rate of response ? therapy w/high HAI
Positive	>10 ⁵	Elevated	IFN vs LAM vs ADV vs ETV

Keeffe et al, 2004

Treatment Algorithm HBeAg – (Pre-core mutant)

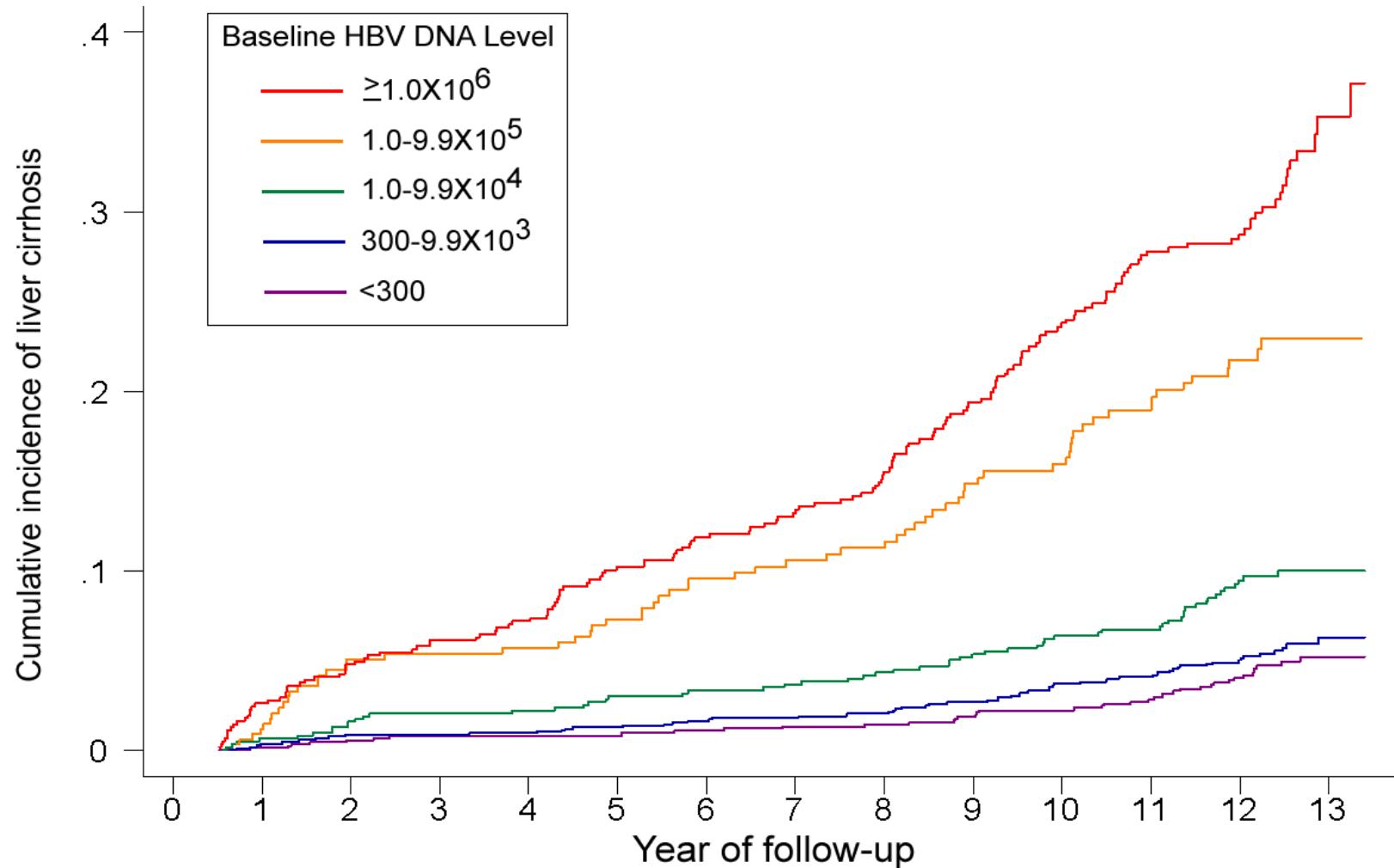
HBeAg Status	HBV DNA	ALT	Possible Strategy
Negative	< 10 ⁴	Normal	Monitor q6-12 months ? therapy w/high HAI
Negative	≥10 ⁴	Normal	Low rate of response ? therapy w/high HAI
Negative	>10 ⁴	Elevated	IFN vs LAM vs ADV vs ETV

Keeffe et al, 2004

Chronic Hepatitis B Special Considerations

- **Cirrhosis**
 - Nucleoside analogue therapy can improve clinical status
 - Interferons contraindicated due to risk of decompensation
- **Liver transplant**
- **HBeAg – pre-core mutants**
- **Immunosuppressed: Prophylaxis warranted**
 - Chemotherapy can reactivate HBV
 - TNF inhibitors reported to reactivate HBV
- **Pregnancy**
 - Consider late trimester prophylaxis in high risk women

Cumulative Incidence of Liver Cirrhosis for Five HBV DNA Categories (n=3,774)



p value for log-rank test, <0.001, Chen et al, DDW, 2005

Lamivudine and Cirrhosis Maintenance Therapy

Variable	Lamivudine	Placebo	Hazard Ratio	p
Disease Progression	7.8%	17.7%	0.45 (.28-.73)	0.001
Increase Child-Pugh	3.4%	8.8%	0.45 (.22-.90)	0.02
HCC	3.9%	7.4%	0.49 (.25-.99)	0.047

Liaw et al, 2004

Lamivudine Decreases Vertical Transmission

- First large-scale study to show that short-term lamivudine decreases mother-to-child transmission

HBsAg(+) pregnant women
HBV DNA > 1000 mEq/mL
(n = 114)

Lamivudine (100 mg/day) from 32 ± 2 weeks of gestation to 4 weeks postpartum (n = 56)

Placebo (n = 59)

All infants received

- HBV vaccine (10 g/0.5 mL)
- HBIg (200 IU, single dose)

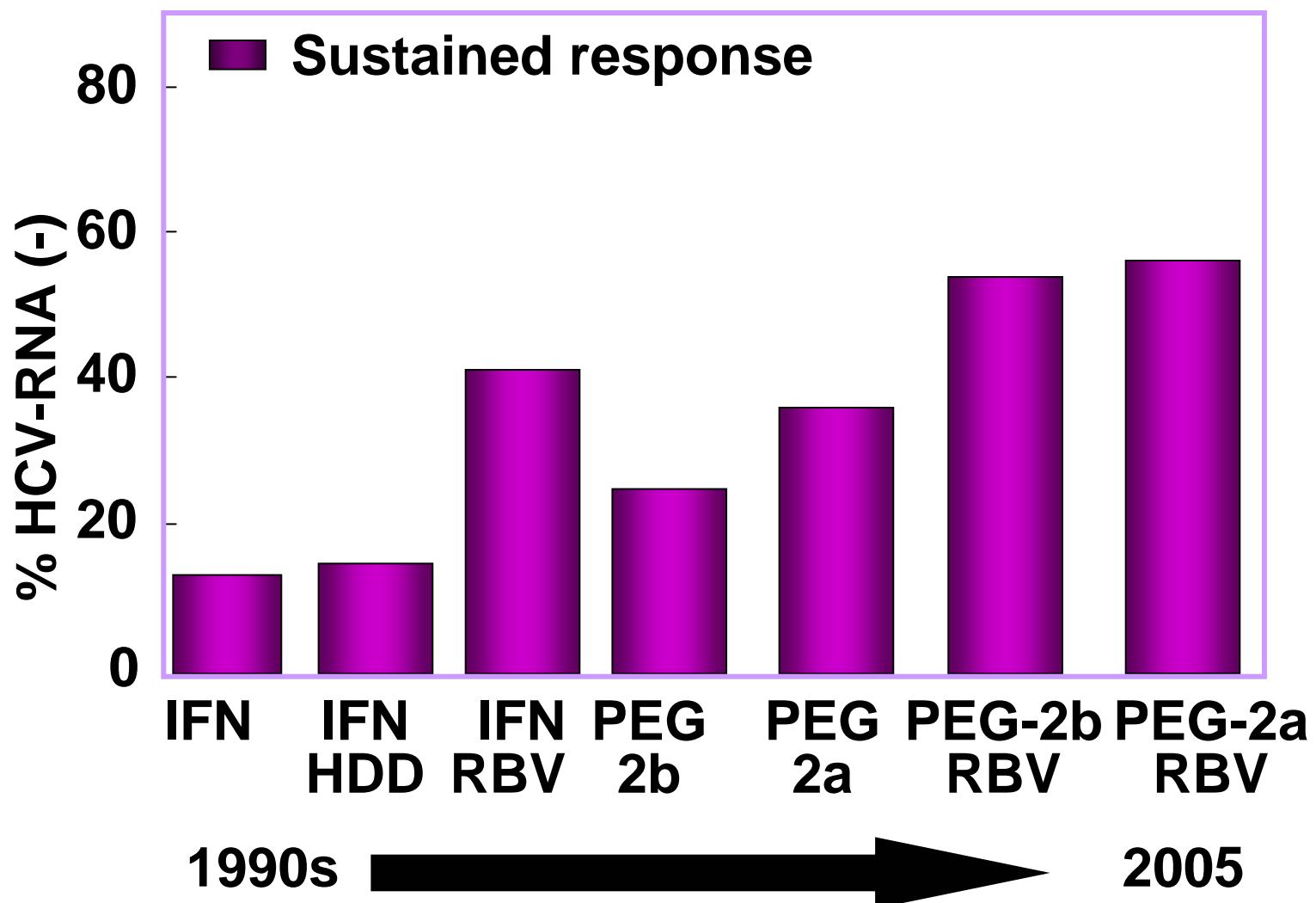
Infant Status at 52 weeks	LAM (n = 56)	Placebo (n = 59)	P Value
HBsAg(+), %	18	39	.014
HBV DNA(+), %	20	46	.003

Therapy for Hepatitis B: 2005 Unanswered Questions

- **What is the best first line agent?**
- **Optimal treatment duration?**
- **What will be the role of combination therapy?**
 - Nucleoside + nucleoside?
 - Nucleoside + interferon?
- **Should patients with normal ALT be treated?**
- **Patience vs Patients: Is watchful waiting appropriate under certain circumstances?**

Evolution of HCV Therapy

Unprecedented Success

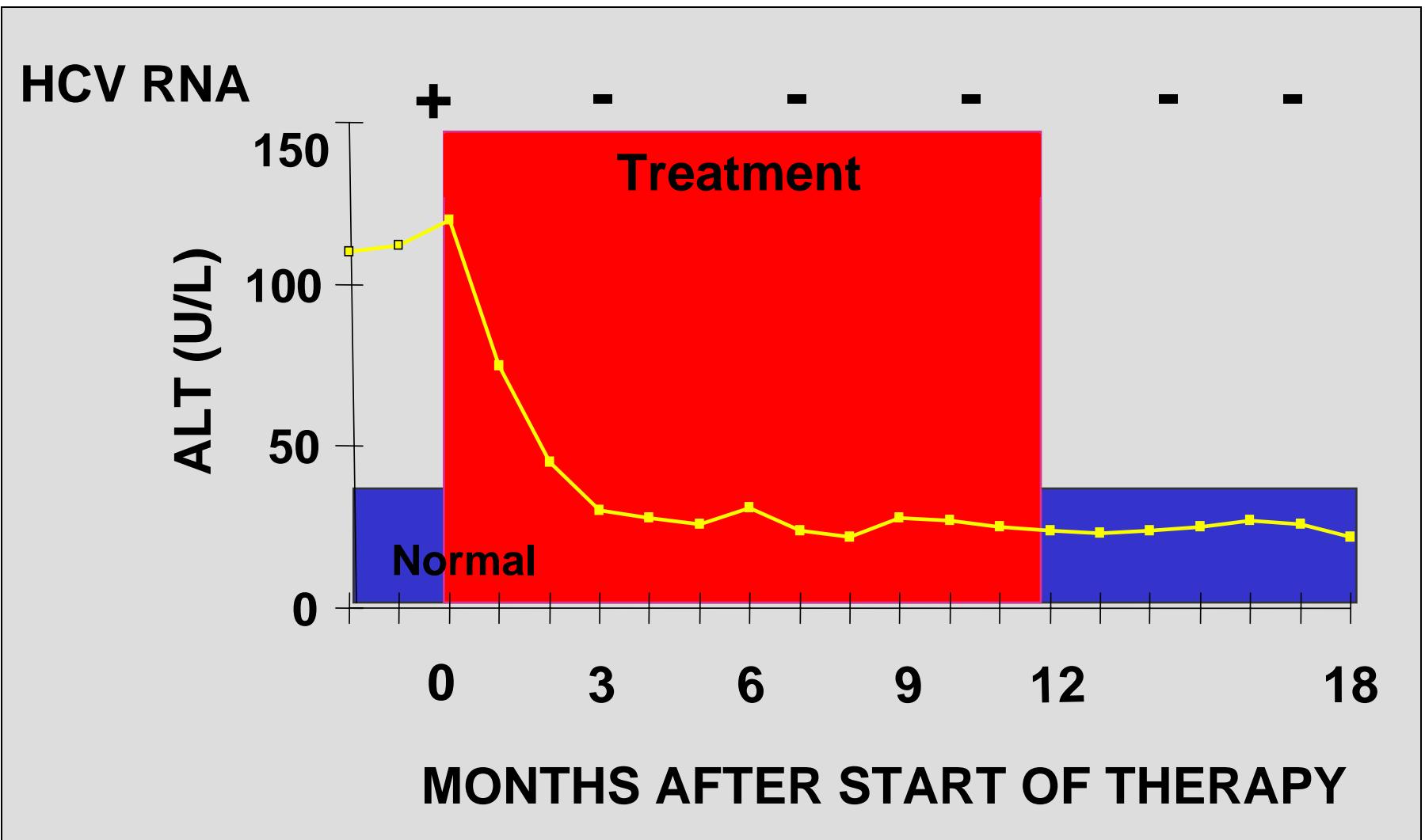




Cured Hepatitis C ??!!??

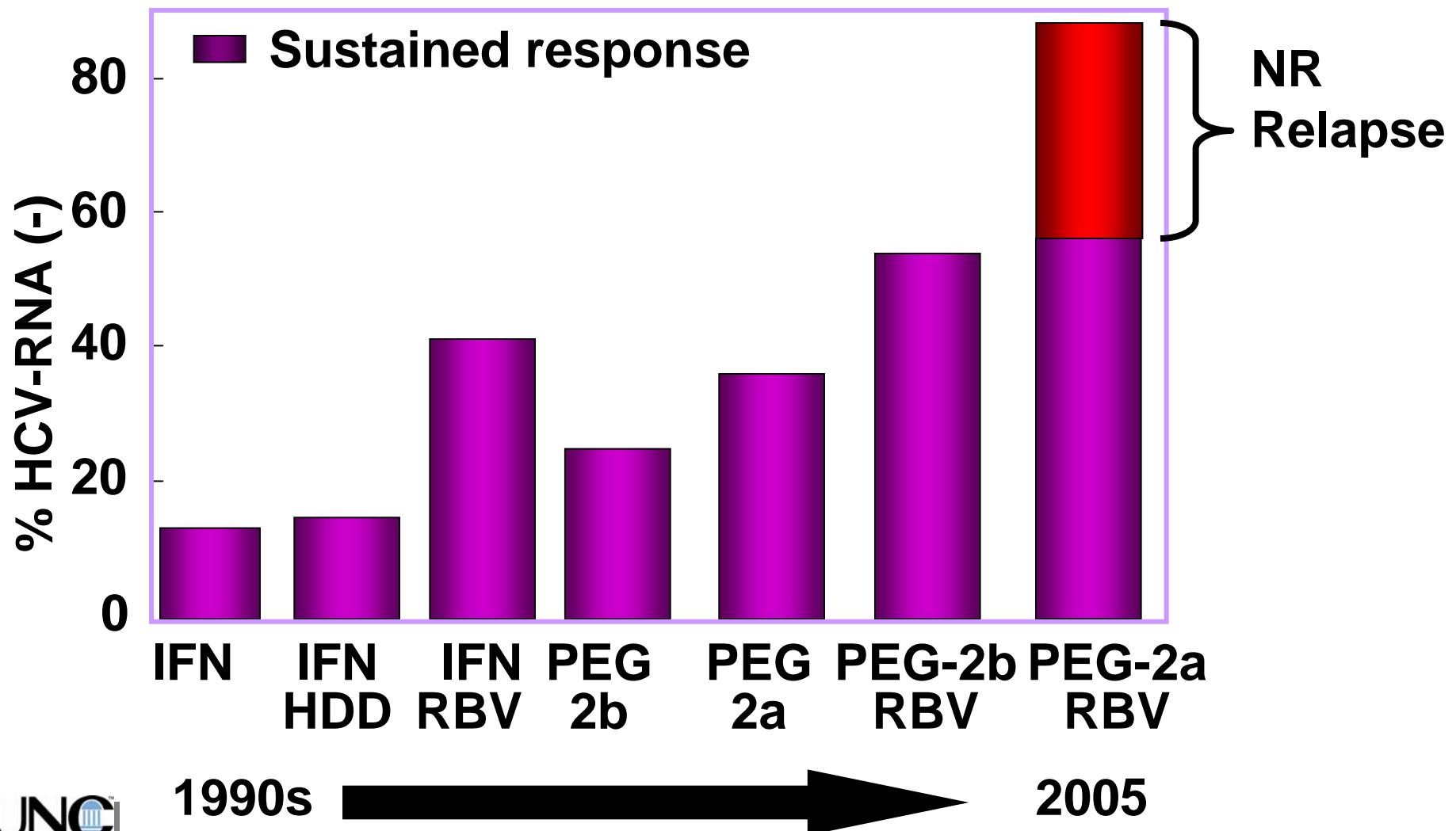
CHRONIC HEPATITIS C

Sustained Response

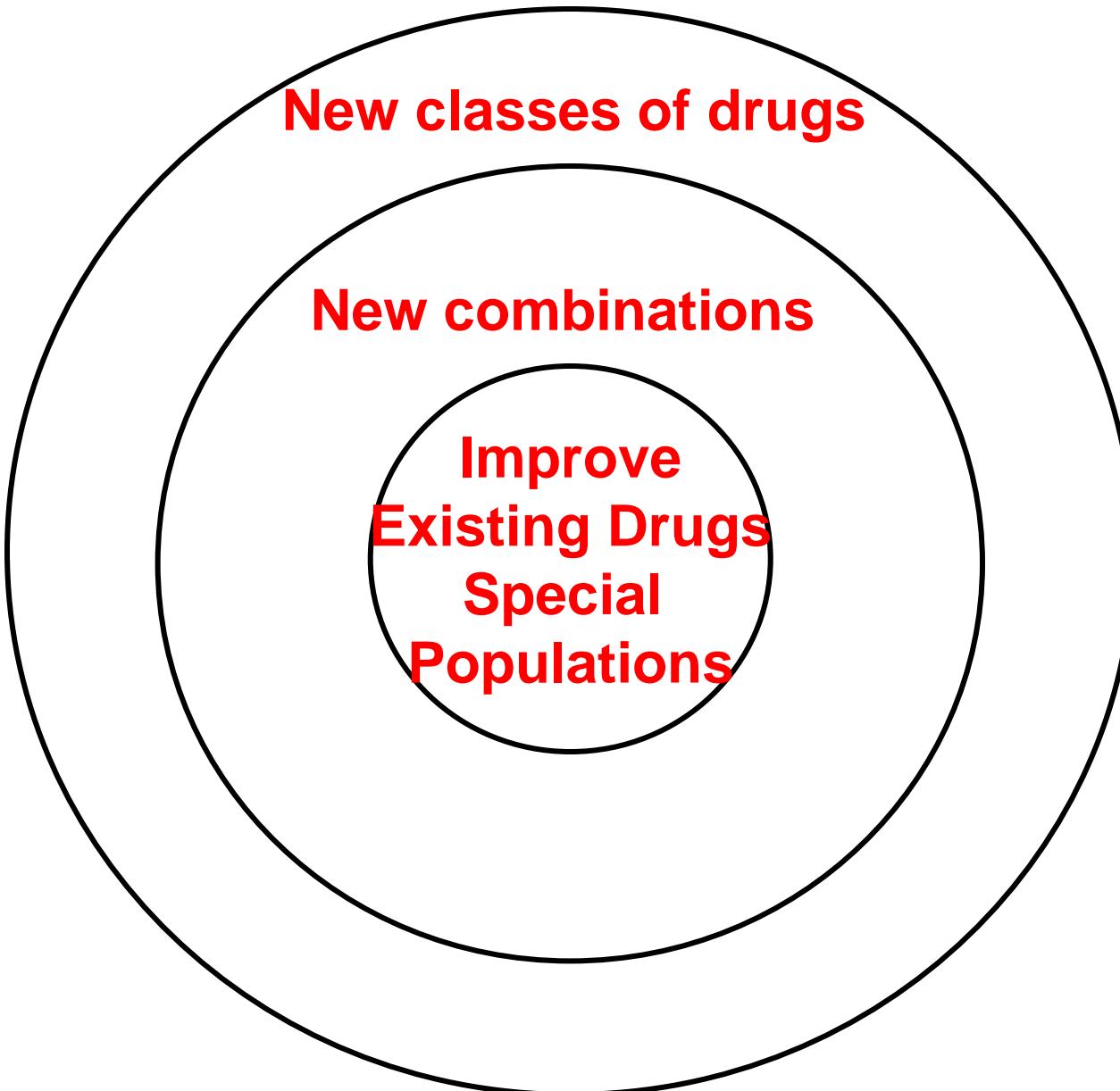


Evolution of HCV Therapy

Driving the Need for Better Therapeutics



Evolution of Therapeutic Approaches



Hepatitis C Therapy

Peginterferon Registration Trials

Agent	RBV Dose (mg/d)	Duration (weeks)	ETR	SVR	Control SVR
PEG-2b (1.5 μ g/kg/week)	800	48	65%	54%	47%
PEG-2a (180 μ g/week)	1000- 1200	48	69%	56%	44%

Manns et al, Lancet, 2001
Fried et al, NEJM, 2002

Side Effects Combination Therapy

- General categories of adverse
 - Fatigue
 - Influenza-like symptoms
 - Neuropsychiatric symptoms
 - Hematologic abnormalities (*Anemia, Neutropenia*)
 - Gastrointestinal disturbances
 - Dermatologic changes
 - Other: Thyroid, cough, retinopathy, pneumonitis

IFN alfa-Induced Behavioral Symptoms

Depressive symptoms	%	Neurovegetative symptoms	%
Depressed mood	60	Fatigue/loss of energy	80
Anhedonia	30	Abnormal sleep	45
Suicidal thoughts	10	Psychomotor retardation	40
Feelings of guilt	5	Abnormal appetite	35
Anxious symptoms		Somatic symptoms	
Tension/irritability	50	Pain	55
Anxious mood	45	Gastrointestinal symptoms	50
Fear	15		
Cognitive symptoms			
Loss of concentration	30		
Memory disturbances	15		
Word-finding problems	15		
Episodes of confusion	10		
Indecisiveness	10		

Special Populations

What is “Special”?

- “*Special*”:
 - *Surpassing what is common or usual*
 - *Distinct among others of a kind*
 - *Peculiar to a specific person or thing*
- “Special populations” in HCV therapy:
 - Not included in registration trials
 - Data is lacking about response to therapy
 - Conventional management may not be applicable
 - **Implies an unmet medical need**
- Populations formerly known as “special”:
 - Normal ALT

Special Populations/Unmet Needs

Primary

- Genotype 1, HVL
- HIV/HCV co-infection
- African Americans
- Liver transplantation
- Renal failure/renal transplant
- Children
- Active substance abusers
 - Alcohol/IVDU

Secondary

- Relapser
- Non-responder
- Intolerant to PEG/RBV
- Contraindications to PEG/RBV

HCV/HIV Co-infection

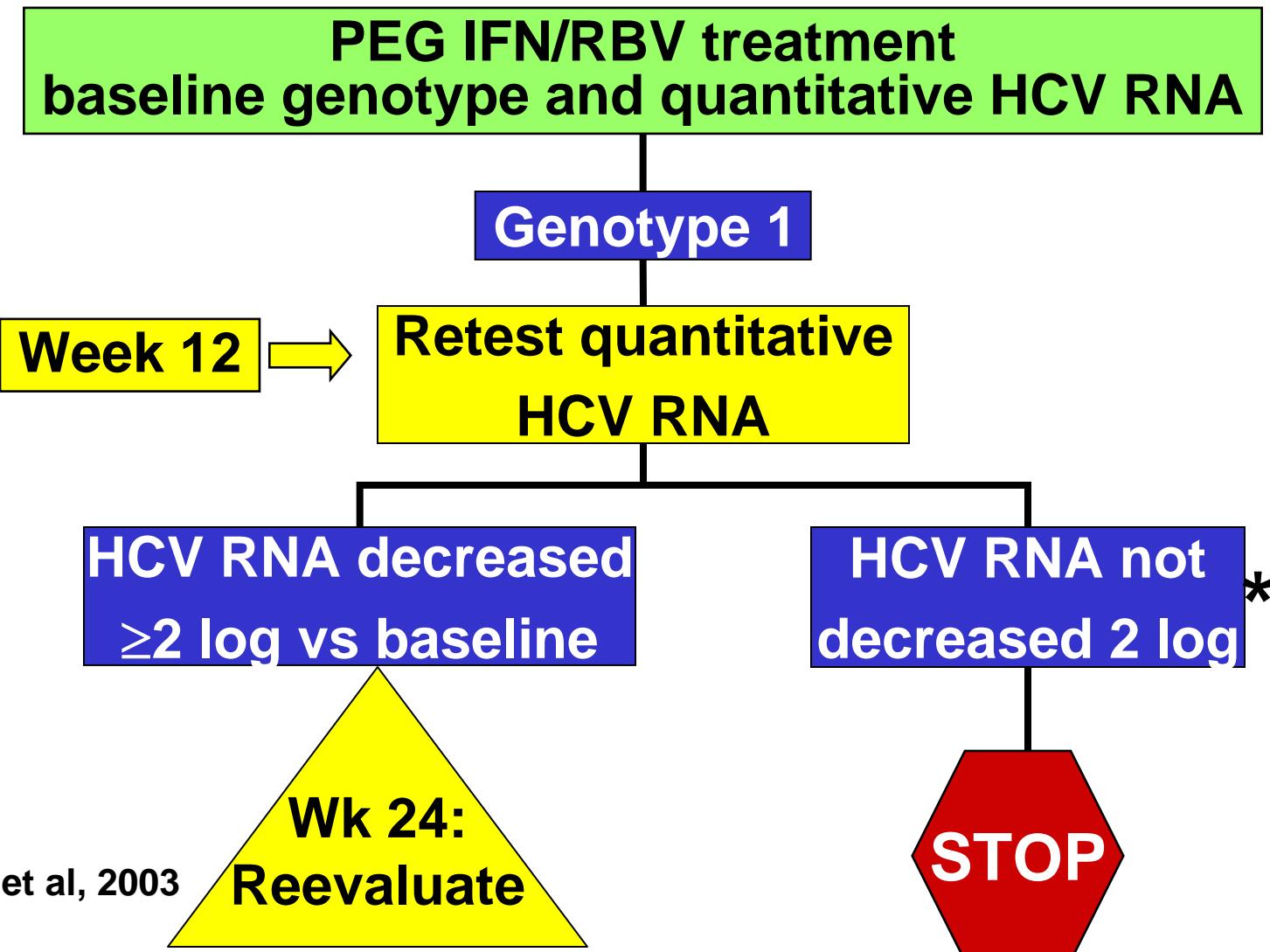
Study	No. Patients	Interferon Agent	RBV Dose	SVR vs Control
ACTG 5071	133	Peg-2a	600- 1000	27% vs 7%
APRICOT	860	Peg-2a	800	40% vs 20%
RIBAVIC	412	Peg-2b	800	26% vs 18%

Chung et al, 2004
Torriani et al, 2004
Carrat et al, 2004

African Americans

Study	No. Patients (AA/CA)	IFN Agent	RBV Dose	SVR AA	SVR CA
Muir et al	100/100	Peg-2b	800	19%	52%
Jeffers et al	78/26	Peg-2a	1000- 1200	26%	39%
VIRAHEP	196/205	Peg-2a	1000- 1200	?	?

Applying EVR Genotype 1



Limitations of EVR

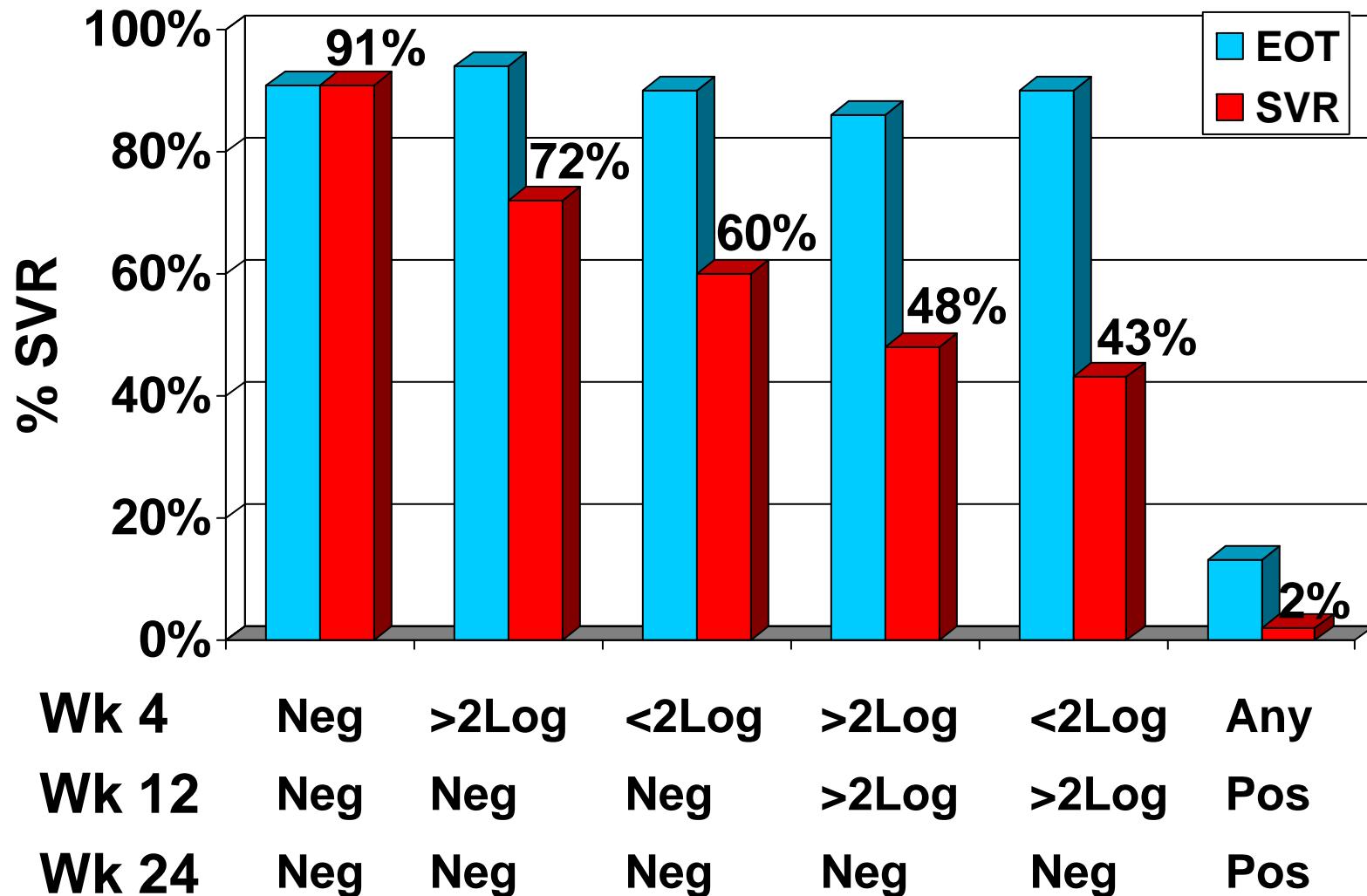
- Developed to identify those without SVR
 - Histologic endpoint
 - Improvement in extrahepatic manifestations
- EVR is a guideline not a law
 - Must be flexible with interpretation

New Applications of Viral Kinetics

- EVR is a useful clinical tool mostly limited to its negative predictive value
- Treatment recommended for 24 weeks for genotype 2 or 3 and 48 weeks for genotype 1
 - Does one size really fit all?
- Evaluation of more detailed viral kinetics has the potential to tailor therapy to an individual's antiviral response

Viral Kinetics and Outcome Importance of Rapid Virological Response

Ferenci et al, 2005 (in press)



Factors Associated with SVR

- **Genotype**
- **HCV RNA level**
- **Histology**
- **Race**
- **HIV co-infection**
- **Adherence**
- **Steatosis**
- **Body weight**
 - Regardless of preparation Peg-2a and Peg-2b have diminished SVR in overweight, high BMI

Options for Non-responders

- **Observation**
- **Retreatment with available agents**
- **Consensus interferon (await phase III trials)**
- **Maintenance therapy (peginterferon)**
 - Preliminary data suggests improvement in portal HTN
 - Reserved for advanced fibrosis/cirrhosis
 - Must demonstrate objective response
 - Long-term safety and efficacy not demonstrated
- **New agents**

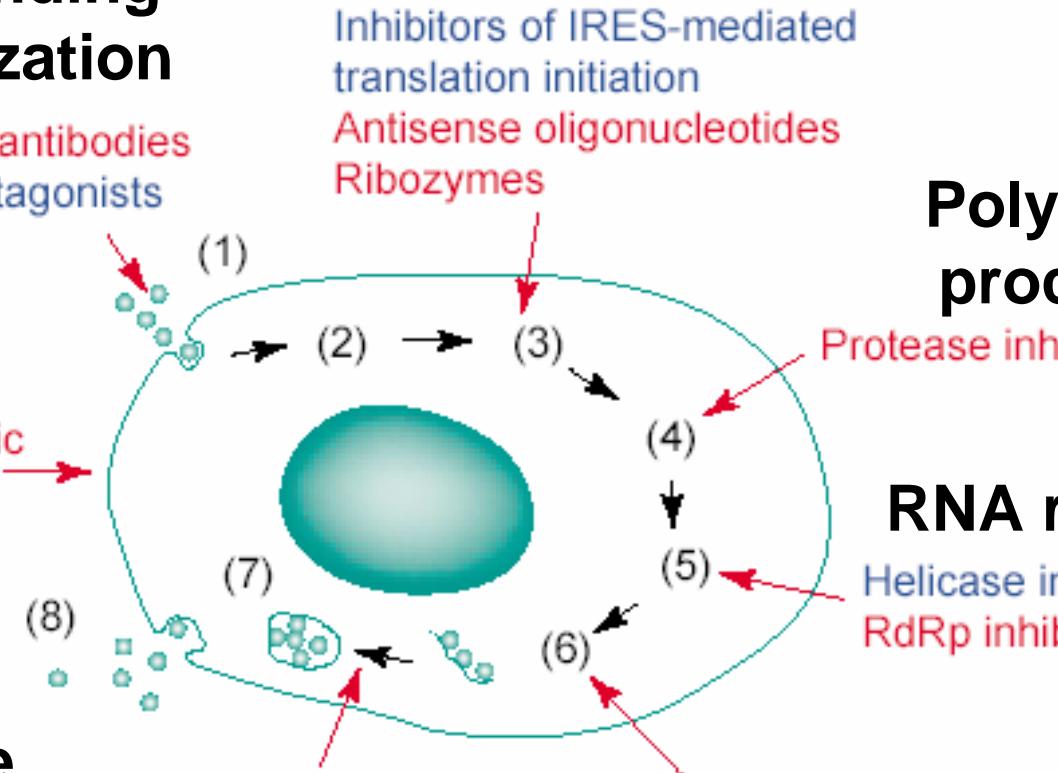
Virus binding Internalization

CD81
LDL
L-SIGN

Neutralizing antibodies
Receptor antagonists

Immunotherapeutic
strategies

Virion Release



Polyprotein processing

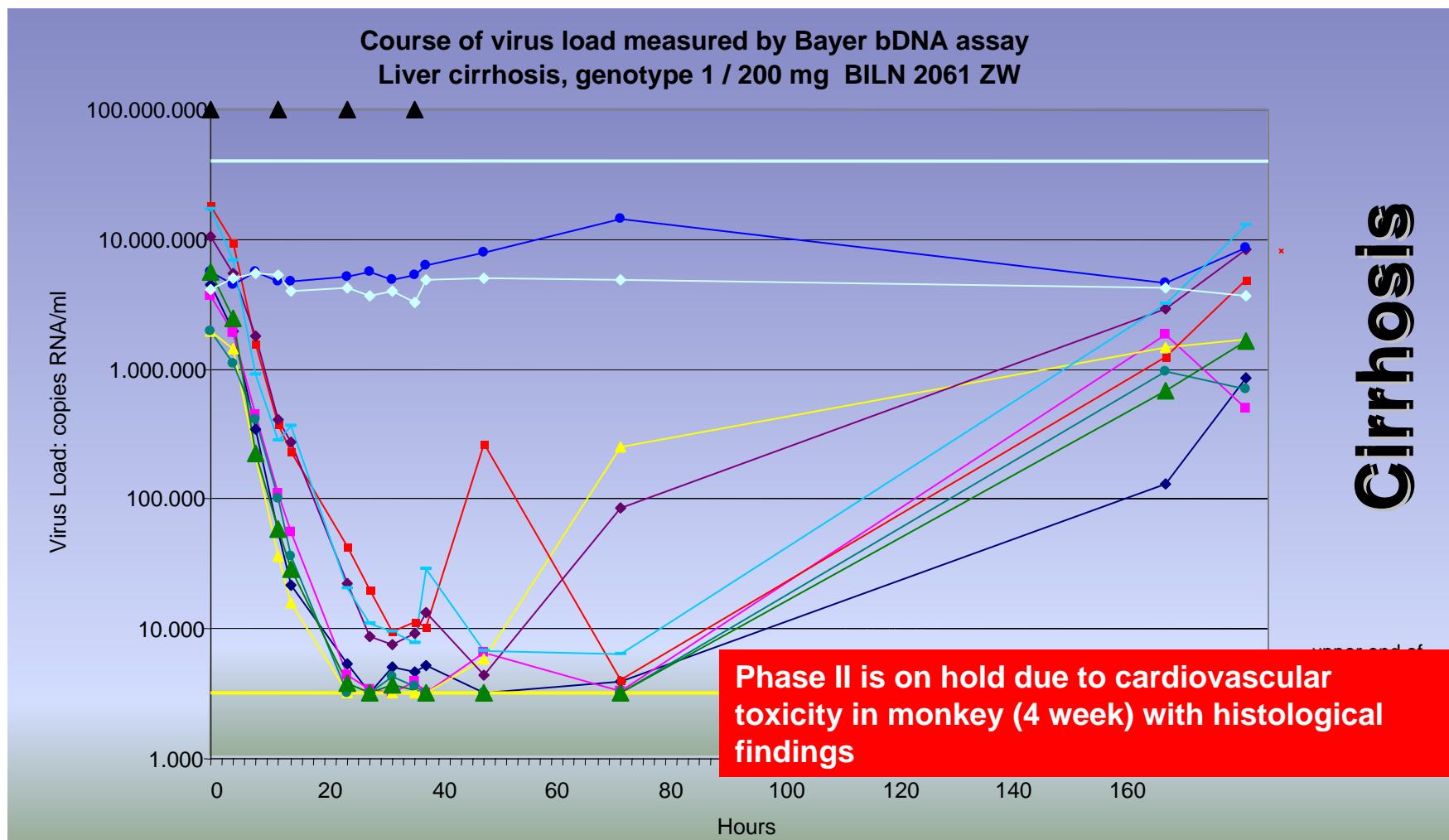
RNA replication

Helicase inhibitors
RdRp inhibitors

Packaging/ Assembly

BILN 2061

Genotype 1, 200 mg bid



HCV Therapy: An Optimist's Perspective Summary

- Current therapies deliver unprecedented ability to cure a chronic viral infection in over half of those treated
- Short-term strategies will tailor therapy to individual needs and patterns of response
- Special populations and those resistant to therapy drive the search for new agents for the treatment of chronic hepatitis C
- New classes of drugs designed to attack specific targets in HCV replication are very promising